

## EDITORIAL

# Postural Orthostatic Tachycardia Syndrome (POTS) – A novel member of the autoimmune family

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Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous disorder of the autonomic nervous system in which a change from the supine position to an upright position causes an abnormally large increase in heart rate or tachycardia (30 bpm within 10 min of standing or head-up tilt). This response is accompanied by a decrease in blood flow to the brain and hence a spectrum of symptoms associated with cerebral hypoperfusion.<sup>1</sup> Many of these POTS-related symptoms are also observed in chronic anxiety and panic disorders, and therefore POTS is frequently under- and misdiagnosed.<sup>2,3</sup> *Lupus* (2016) **25**, 339–342.

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The estimated prevalence of POTS is at least 170/100,000. This estimate was based on the finding that 40% of patients with chronic fatigue syndrome (CFS) also suffer from POTS.<sup>4</sup> Indeed, CFS is a frequent and major complaint in POTS,<sup>5</sup> and a substantial overlap between POTS and CFS has been consistently reported in the literature.<sup>5–8</sup> Despite its common prevalence and significant negative impacts on the population, the causes of POTS and CFS remain unclear and there are currently only limited effective treatments for these complex conditions. Genetic as well as non-genetic factors such as trauma, bacterial or viral infection, and pregnancy may predispose to POTS.<sup>1,3,9,10</sup> In addition, it is becoming increasingly recognized that POTS and CFS can also be triggered by various medications (i.e., antihypertensive drugs, antipsychotics),<sup>1</sup> and by vaccines.<sup>11–15</sup>

An autoimmune mechanism has been suggested as a causal mechanism in both POTS and CFS,<sup>2,3,7,14,16</sup> due to frequent findings of autoantibodies (including ANA) in POTS/CFS patients.<sup>17–22</sup> More specifically, ganglionic A3 acetylcholine receptor antibodies are found in at least one in seven POTS patients.<sup>7</sup> Moreover,

various autoantibodies, including those directed against cardiac proteins,<sup>21</sup>  $\beta$ 1/2-adrenergic, M2/3 muscarinic<sup>23</sup> and N-type acetylcholine receptors,<sup>7</sup> have been identified in POTS patients, strengthening the idea of POTS as member of the autoimmune autonomic neuropathies family. The presence of autoantibodies may predispose the heart and the autonomic nervous system to vulnerable pathologic stimuli, and an adverse autoimmune reaction may trigger possible inflammatory responses with injury to the myocardium as well as to the peripheral autonomic nerves.<sup>21</sup> In addition, as shown by our group and others,<sup>24,25</sup> immunoglobulins can penetrate/internalize into living susceptible specific cells, via diverse pathways of endocytosis involving different parts of the molecule. Following endocytosis, the immunoglobulin may target different intracellular component of cellular signaling, leading to dysfunction of the specific cell. These scenarios may elucidate the contribution of pathogenic autoantibodies to the pathophysiology of diverse autoimmune diseases, including POTS.

POTS, CFS, and autoimmune disorders have a strong female predominance,<sup>2,3,9,26</sup> which further suggests a common etiological denominator. The clinical significance of the positive ANA test in CFS patients is probably due to differential diagnoses of systemic lupus erythematosus (SLE) and other diffuse connective tissue diseases. Indeed, both POTS and CFS frequently co-occur with

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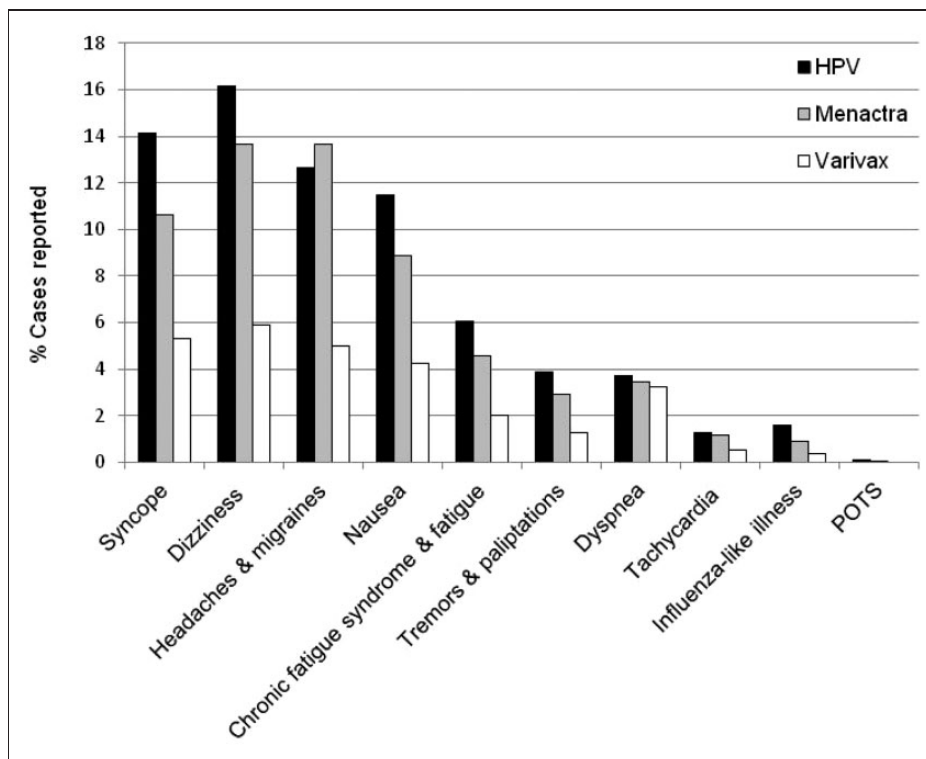
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systemic autoimmune disorders including multiple sclerosis,<sup>27</sup> Sjogren's syndrome,<sup>28</sup> SLE,<sup>1,29</sup> and Raynaud's phenomenon.<sup>30</sup> Petri et al.,<sup>31</sup> for example, found that 74% of SLE patients with fibromyalgia/CFS also have neurally-mediated hypotension.

With reference to post-HPV vaccine POTS, it is probable, as emphasized by Blitshteyn,<sup>12</sup> that some patients are simply undiagnosed or misdiagnosed, which leads to underreporting and a paucity of data on the incidence of POTS following vaccination. Analysis of the US Vaccine Adverse Event Reporting System (VAERS) database substantiates this concern.<sup>32</sup> In particular, although the majority of POTS-related symptoms were reported in 4–16% of HPV vaccine recipients, POTS was only reported in 0.07% of cases (Figure 1). Compared to two other vaccines routinely given to adolescents and young individuals in the US (Menactra and Varivax), HPV vaccines had the highest rate of

both POTS and CFS-related complaints. On average, the number of POTS/CFS symptoms was three to five times greater in HPV compared to Varivax vaccine recipients. A relatively high frequency of POTS/CFS symptoms reports were also recorded for the Menactra vaccine, suggesting that the risk of these syndromes may vary between different vaccines. If the associated symptoms were psychogenic and not related to a specific vaccine but rather a reaction to the injection procedure itself,<sup>33,34</sup> one would expect a more even distribution of reports with different vaccines. As shown in Figure 1, this is clearly not the case. Because both POTS and CFS can be severely disabling conditions,<sup>1,5,13,15,16,35</sup> a more thorough follow-up of patients who present with relevant complaints post-vaccination is recommended in order to determine the true incidence of these syndromes with particular vaccines.

There are several plausible explanations for the appearance of abnormal cardiac manifestations,



**Figure 1** Age-adjusted rate of POTS/CFS related adverse reactions reported following HPV, Menactra meningococcal polysaccharide diphtheria toxoid conjugate and Varivax Varicella vaccines in the US reported to the Vaccine Adverse Event Reporting System (VAERS) as of February 13, 2013.<sup>32</sup> The VAERS database was searched using the following criteria: 1) symptoms: syncope (general, exertional, postural); headaches (including migraines); nausea; chronic fatigue syndrome (including general fatigue); tremors and palpitations; dyspnea (general, exertional, at rest); tachycardia (including tachyarrhythmia, tachycardia paroxysmal, heart rate abnormal, heart rate increased, heart rate irregular); influenza-like illness (including viremia, viral infection); POTS; 2) vaccine products: HPV, HPV2 (human papilloma virus bivalent), HPV4 (human papilloma virus types 6,11,16,18); MNQ (Meningococcal vaccine Menactra); Varcel (Varivax-Varicella virus live); 3) gender (all genders); 4) age (6–29 years; target age group for HPV, Menactra, and Varivax vaccines); 5) territory (the United States); 6) date vaccinated (2007–2013; HPV vaccine post-licensure period).

including death, following HPV vaccination. Namely, in exploring the primary sequence of the HPV 16 major capsid L1 protein (one of the four antigens in Gardasil) for peptide sharing with human proteins, Kanduc found that 34 pentamers from the HPV viral capsid protein are shared with human proteins that,<sup>36</sup> when altered, have been linked to arrhythmias, cardiovascular diseases and sudden death. In particular, 9 out of the 34 viral pentamers are present in the human protein, Titin, alterations of which have been linked to cardiac failure and sudden cardiac death. Other significant matches include components of intercellular desmosome junctions such as plakophilin-2, desmoplakins, and desmocollin-2. Defects in these desmosomal proteins have been reported in arrhythmogenic right ventricular cardiomyopathy (ARVC),<sup>37,38</sup> which as mentioned above, has previously been linked to sudden cardiac death during sleep.<sup>39-41</sup> Another significant match with HPV-16L1 sequence, is the voltage-dependent L-type calcium channel subunit alpha-1C, alterations of which cause the Brugada syndrome, which is another arrhythmogenic disorder associated with high-risk nocturnal arrhythmias.<sup>42,43</sup> In addition, MYH6 and MYH7, which are the two isoforms of the myosin heavy chain that are specifically located in the cardiac muscle and whose alterations can lead to sudden cardiac death, also show sequence similarity with HPV-16L1.<sup>36</sup>

In summary, the cited investigation by Kanduc confirms and extends previous reports describing a high level of perfect peptide matching between bacterial/viral antigens and the human proteome.<sup>36,44-47</sup> Furthermore, it suggests that possible immune cross-reactions deriving from utilization of HPV L1 in current HPV vaccines might be a risk for cardiovascular abnormalities (and fatalities), as well as POTS. The author emphasizes the necessity for better understanding of potential antigen cross-reactivity (which at present is lacking), since failure to analyze and minimize levels of cross-reactivity may lead to harmful, even lethal, post-vaccination events.<sup>36</sup>

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